

## Amyloid-beta Increases Capillary Bed Density in the Adult Zebrafish Retina.

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### Public Summary:

Alzheimer's disease affects over 5 million people in the USA. Although deposits of the peptide amyloid-beta are a critical feature of the pathology, the normal physiological role of this peptide remains unclear. In this publication we show that amyloid-beta plays a role in blood vessel density in the adult zebrafish retina. This point is significant to understanding Alzheimer's disease because the brain deposits of amyloid-beta, commonly known as plaques, are surrounded by tissue that has very dense blood vessel networks, aka as hyper-vascular. Interestingly, Abeta is also found in aggregates associate with macular degeneration, a common cause of blindness in the elderly, and our findings suggest there may be vascular similarities between the neurodegeneration that occurs in Alzheimer's disease and macular degeneration. Some of vessels treated with Abeta formed loops and dead ends that are inefficient at providing a proper blood supply to cells in those areas. As an allegory, we suggest it is like adding extra sprinklers to a green lawn: while ten sprinklers might work well a hundred could result in only trickles from branch with brown (under-nourished) patches in between – where Alzheimer's pathology can take hold and eventually form plaques. Findings from this study help us understand how monomeric A $\beta$  affects local blood vessel density, which may be an early event in Alzheimer's etiology. Knowledge arising from this research will contribute to the development of new and effective therapies for this terrible disease. CIRM-funded research supported group interactions in Dr. Ethell's laboratory that contributed to this breakthrough, and helped defray costs of publication.

### Scientific Abstract:

**PURPOSE:** Amyloid-beta (Abeta) is an endogenous peptide that becomes dysregulated in AMD and Alzheimer disease. Both of these disorders are marked by extracellular deposits that contain Abeta, highly branched capillary networks, and neurodegeneration. Although Abeta has been implicated in AMD and Alzheimer pathology for decades, its nonpathological function has remained unclear. We recently showed that high levels of monomeric Abeta induce blood vessel branching in embryonic zebrafish brain, and here we report that a similar mechanism may contribute to aberrant blood vessel branching in the retina of adult zebrafish. **METHODS:** Transgenic zebrafish expressing enhanced green fluorescence protein (EGFP) in their endothelial cells were sedated and small intraocular injections of PBS were made into one eye and either Abeta or gamma-secretase inhibitor were injected into their opposite eye. A week later, the eyes were enucleated and high resolution maps of the retina vasculature were created using confocal microscopy. Comparisons were made between the treatment groups using the general linear model ANOVA. **RESULTS:** We found that Abeta significantly affects capillary blood vessels in the retina. Small volumes of Abeta injected into the eyes of adult zebrafish induced the formation of significantly more endothelial tip cells and capillary bridges-some with loops-near the circumferential vein. These effects were dose-dependent and increased capillary bed density, though there was no effect on larger arterial vessels. **CONCLUSIONS:** This study reveals a previously unknown role for Abeta in regulating capillary bed density, providing new insight into the normal biological function. Abeta will help in the development of therapeutic interventions for AMD and Alzheimer disease.

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